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PROCESS FOR THE PRODUCTION OF CROSS-LINKED GELATIN MICROBEADLETS

FIELD OF THE INVENTION

The present invention relates to a process for the production of beadlets with a high concentration of an active ingredient selected from a fat soluble vitamin, a carotenoid and a polyunsaturated fatty acid, to the resulting beadlets and to compositions containing them.

SUMMARY OF THE INVENTION

More particularly the invention provides a process for the production of cross-linked beadlets containing one or more active ingredients selected from the group of a fat-soluble vitamin active material, a carotenoid and a polyunsaturated fatty acid,
the process comprising treating a dry particulate form at a temperature in the range of from 90°C to 140°C for a time period of from 30 seconds to 30 minutes or from 1 minute to 10 minutes or from 3 minutes to 7 minutes.

DETAILED DESCRIPTION

Examples of a fat-soluble vitamin active material include vitamin bearing oils, provitamins and pure or substantially pure vitamins, both natural and synthetic, or chemical derivatives thereof and mixtures thereof. Of particular interest is a vitamin selected from the group of vitamins A, D, E and K, and derivatives thereof. For example, the term "Vitamin E" includes synthetically manufactured tocopherols or a mixture of natural tocopherols. Examples of vitamin derivatives include vitamin A acetate, vitamin A palmitate and vitamin E acetate. An example for a vitamin D-active material is vitamin D_3. As a particular example, the process of the present invention may result in a beadlet containing a vitamin A-active material and a vitamin D-active material, e.g. vitamin A and vitamin D_3.

In one embodiment the process of the invention may involve Vitamin A as fat-soluble vitamin active material in a total concentration in the range of from 500,000 IU vitamin A/g beadlet to 1,500,000 IU vitamin A/g beadlet, in the range of from 750,000 IU vitamin A/g beadlet to 1,500,000 IU vitamin A/g beadlet, or in the range of from 750,000 IU vitamin A/g beadlet to 1,300,000 IU vitamin A/g beadlet, e.g. vitamin A may be present in the beadlet in a total concentration of 500,000 ± 35,000 IU active ingredient/g beadlet, 750,000 ± 35,000 IU active ingredient/g beadlet, of 1,000,000 ± 35,000 IU active ingredient/g beadlet, or of 1,100,000 ± 35,000 IU active ingredient/g beadlet. Vitamin D as fat-soluble vitamin active material may be present in the range of from 100,000 IU vitamin D/g beadlet to 500,000 IU vitamin D/g beadlet or in the range of from 100,000 IU vitamin D/g beadlet to 200,000 IU vitamin D/g beadlet, vitamin E as fat-soluble vitamin active material may be present in the range of from 50 % to 75 % vitamin E.

Examples for a carotenoid include β-carotene, lycopene, zeaxanthin, astaxanthin, lutein, capsanthin and cryptoxanthin.

In one embodiment the process of the invention may involve a carotenoid in a total concentration in the range of from 5 % to 20 %, in the range of from 5 % to 15 %, or in the range of from 7 % to 15 %.

Examples for a polyunsaturated fatty acid, as triglyceride and/or ethylester, include arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid and γ-linolenic acid and/or ethylester.

In one embodiment the process of the invention may involve a polyunsaturated fatty acid as triglyceride in a total concentration in the range of from 20 % to 50 %, in the range of from 25 % to 40 %, or in the range of from 28 % to 38 %.

The dry particulate forms used in the process of the present invention may be prepared by any procedure known to the skilled artisan, e.g. by forming an aqueous emulsion containing the active ingredient, an emulsifier, a texturing agent and a reducing sugar, followed by converting the emulsion to a dry particulate form containing the non-aqueous constituents of said emulsion.

Examples for an emulsifier are gelatine and ascorbyl palmitate. Gelatine is an emulsifier which at the same time functions as a texturing agent. Any gelatine which has a "bloom" in the range of practically zero to about 300 can be employed in the practice of the present invention. Both Type A and Type B gelatine can be employed. The preferred gelatine used

is Bloom 140, but gelatine Bloom 30 or Bloom 75 would be possible as well. In the presence of gelatine no additional texturing agent may be necessary.

The concentration of the emulsifier depends on the kind of emulsifier used, e.g. gelatine may be present in a concentration in the range of from 25 % to 35 %, or less.

Examples for a texturing agent beyond gelatine include carrageenan, modified starch, modified cellulose, xanthan gum, acacia gum, pectins, guar, caroub gums, maltodextrines and alginates.

The concentration of the texturing agent depends on the kind of texturing agent used and may be, e.g., in the range of from 0 % to 15 %.

Examples for a reducing sugar are fructose, glucose, lactose, maltose, xylose, arabinose, ribose and sucrose. One type of sugar may be used or a mixture of two or more sugars. The reducing sugar may be added as such or in the form of a syrup, e.g. fructose or glucose syrop.

The concentration of the reducing sugar depends on the kind of reducing sugar used and may be, e.g., in the range of from 2 % to 10 %, or in a ratio of gelatine:sugar in the range of from 3:1 to 7:1, e.g. 5:1.

Small quantities of other ingredients may be incorporated including antioxidants like 6-ethoxy-1,2-dihydroxy-2,2,4-trimethylquinoline (ethoxyquine), 3,5-di-tertiary-4-butyl hydroxytoluene (BHT)and 3-tertiary butyl-hydroxyanisole (BHA), humectants such as glycerol, sorbitol, polyethylene glycol, propylene glycol, extenders and solubilizers.

As a typical example gelatine and a suitable sugar may be dissolved in water previously mixed with glycerin. The dissolution may last at 65-70°C for, e.g., about 30 minutes. Then, e.g., the vitamin A with the antioxidant may be added and emulsified. The pre-emulsification may be done with a colloid mill, e.g., based on a rotor/stator principle. The pre-emulsification may be hold for between 15 and 30 minutes at a rotation speed of the rotor between 500 and 1500 rpm and may then pass through a high pressure homogeniser resulting in a conversion of the emulsion to fine droplets.

In one example the conversion of emulsion droplets to "set up" particles may be attained by introducing a spray of emulsion droplets into an agitated cloud or suspension in air of the particles of the finely dispersed powder, e.g. by forcing the emulsion through a revolving spray head into a suspension in air of the powdered material, contained in and agitated by a revolving cylindrical drum, the drum and the spray head rotating in opposite

directions so that the cloud or suspension of the powder in air is swirling in a sense of rotation opposite to the entering emulsion spray.

Examples of the finely dispersed powder used in the process to collect/coat the droplets of the emulsion include polysaccharides such as starch and modified starch, and calcium silicate alone or a mixture of calcium silicate with one of the following mixture components: microcrystalline cellulose, magnesium silicate, magnesium oxide, stearic acid, calcium stearate, magnesium stearate, hydrophilic silicic acid and kaolin. Coatings which consist of calcium silicate alone are preferred. The calcium silicate may be present wholly or partially in the form of the hydrate.

The calcium silicate particles are especially suitable when they have a size of less than 0.2 μm, especially less than 0.1 μm, and a specific surface of at least about 80 m^2/g to about 180 m^2/g, preferably of about 95 m^2/g to 120 m^2/g, and are agglomerated to aggregates having an average size of about 5-30 μm, preferably 5-20 μm. The SiO_2/CaO ratio lies between 1.65 and 2.65.

In coatings which consist of calcium silicate alone, the amount of calcium silicate may be in the range of from 2 wt.% to 12 wt.%, preferably in the range of from 4 wt.% to 9 wt.%.

In coatings consisting of a mixture of calcium silicate with one or more of the aforementioned mixture components, the amount of the calcium silicate mixture may be in the range of from 5 wt.% to 25 wt.%.

Optionally, the resulting dry particulate forms may be separated from the remaining finely dispersed powder. This may be accomplished by operations which are conventional per se, including, e.g. simply to feed the mixture of powder and dry particulate forms to a shaking screen of a size selected to retain the dry particulate forms while passing the collecting powder.

For further processing those dry particulate forms containing the active material are preferred having a moisture content of less than 10 % and preferably between about 4 to 6 percent. If the moisture content is higher the dry particulate forms may be dried to the desired moisture content by various methods, e.g. by exposing them to air at room temperature or by moderate heating in a drying oven at 37°C to 45°C.

The heat treatment may, e.g., be achieved in a batch or in a continuous process where the beadlet residence time and temperature are controlled.

In the case of a fluid bed process, the beadlet is added either at the beginning in the case of the batch process or constantly in the case of a continuous fluid bed in a hot air or nitrogen stream having a temperature between 100 and 200°C, preferably between 130-160°C. The beadlet temperature is raised in a few second to one minute above 100°C enabling a quick and efficient reaction. The beadlet is ready after 5 to 10 minutes. The beadlet is cooled at the end of the treatment.

In the case of a continuous flash treatment, the beadlet is fed continuously into a hot gas stream having a temperature between 100 and 200°C, preferably between 130-160°C. The beadlet can be moved by mechanical stirring, e.g., above 300 rpm. The wall of the vessel used to make this thermal treatment can also be heated to a temperature in the range of from 110 to 180°C. The desired crosslinking of the beadlet may be reached in a time in the range of from 30 seconds to 10 minutes or from 1 minute to 10 minutes, with a maximum beadlet temperature in the range of from 90°C to 140°C, preferably from 105°C to 125°C.

The beadlet forms resulting from the inventive process have a core and a surface region, wherein the loss of active ingredients in the surface region is reduced, and are also an object of the present invention.

Therefore, the present invention further provides a beadlet form having a core and a surface region, wherein the core region contains, in a high concentration, one or more active ingredients selected from the group of a fat-soluble vitamin active material, a carotenoid and a polyunsaturated fatty acid, and the surface region contains less than 10 % of the total active ingredient content, preferably less than 5 % of the total active ingredient content.

In one embodiment the present invention provides a beadlet form containing one or more active ingredients selected from the group of Vitamin A in a total concentration in the range of from 800,000 IU vitamin A/g beadlet to 1,500,000 IU vitamin A/g beadlet or in the range of from 950,000 IU vitamin A/g beadlet to 1,250,000 IU vitamin A/g beadlet, in a total concentration in the range of from 100,000 IU vitamin D/g beadlet to 500,000 IU vitamin D/g beadlet or in the range of from 100,000 IU vitamin D/g beadlet to 200,000 IU vitamin D/g beadlet, vitamin E in a total concentration in the range of from 50 % to 75 %, a carotenoid in a total concentration in the range of from 5 to 20% and a polyunsaturated fatty acid in a total concentration in the range of from 5 to 50%, wherein the surface region contains less than 10 % of the total active ingredient content. In another embodiment the surface region contains less than 5 % of the toltal active ingredient content.

The beadlets are characterized by high stability and potency. They exhibit high stability when pelletized, e.g. they withstand the temperature, moisture and pressure of a feed pelleting process without losing their physical integrity. They are water insoluble and maintain their properties in relation to bioavailability.

Typical examples of beadlets of the present invention may, e.g. have the following components: 30 % to 45 % of vitamin A, 0 % to 2 % of vitamin D_3, 5 % to 15 % of 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (EMQ), 25 % to 35 % of gelatine, 5 % to 10 % of fructose, 2 % to 10 % of glycerine, 5 % to 10 % of calcium silicate, 0 % to 25 % of corn starch, 0 % to 1 % of edible fat, and water.

Example 1: Preparation of beadlets containing 1,000,000 IU vitamin A/g beadlet plus 200,000 IU vitamin D_3/g beadlet

Approximately 90 parts of gelatine Bloom 140 and 18 parts of fructose were dissolved in 313.2 parts of water (containing 23.2 parts of glycerin) by heating at 65°C. 158 parts of Vitamin A containing 24% ethoxyquin (assay 2.1 Mio. IU vitamin A per g) and 3.5 parts of vitamin D_3 (assay 20 Mio. IU vitamin D_3 per g) were then mixed with the resulting matrix, followed by pre-emulsification.

The beadlet was sprayed using as finely dispersed powder calcium silicate. The average particle size of the beadlet was in the range of from 200 µm to 300 µm.

The beadlet was divided into two groups: one group was treated using a classical heated slow mixer without sufficient control of the thermal history of the beadlet, and the other group was treated by a fluidized bed, i.e. a batch process with an apparatus where the temperature and residence time of the beadlet can be controlled. The results are compared in the following table:

	heated slow mixer	fluidized bed
Vitamin A content after crosslinking (IU/g)	1,025,000	1,050,000
Vitamin A Loss (%)	3-4	0-1
Surface vitamin A (%)	8-10	1-2
Crosslinking grade (%)	76%	82%

In the fluidized bed the temperature was controlled between 100 and 115°C for 5 minutes. In the heated slow mixer, the beadlet was heated for about 15 minutes at a temperature raising from 90°C to 124°C.

Example 2: Preparation of beadlets containing 1,000,000 IU vitamin A/g beadlet

Approximately 100 parts of gelatine Bloom 140 and 20 parts of fructose were dissolved in 308.2 parts of water (containing 13.2 parts of glycerin) by heating at 65°C. 170 parts of Vitamin A containing 24% ethoxyquin (assay 2.1 Mio. IU vitamin A per g) were then mixed with the resulting matrix, followed by pre-emulsification.

The beadlet was sprayed using as finely dispersed powder calcium silicate. The average particle size of the beadlet was in the range of from 180 µm to 270 µm.

The beadlet was divided into three groups: the first group was treated using a classical heated slow mixer as in Example 1, the second group was treated by a fluidized bed as in Example 1, the third group was treated by a continuous flash treatment in diluted phase wherein the flash treatment is ensured by a combination of pneumatic transport and mechanical transport.. The results are compared in the following table:

	heated slow mixer	fluidized bed	flash treatment
Vitamin A content after crosslinking (IU/g)	1,119,000	1,146,000	1,143,000
Vitamin A Loss (%)	3-4	0-1	0-1
Surface vitamin A (%)	8-10	2-2.5	3-5
Crosslinking grade (%)	50-80	50-80	50-80

In the fluidized bed the temperature was controlled between 110 and 120°C for 5 minutes. In the flash treatment, the beadlet was treated for 1 to 4 minutes at a temperature raising from 115°C to 125°C. In the heated slow mixer, the beadlet was heated for about 20 minutes at a temperature raising from 70°C to 124°C.

Example 3: Stability of beadlets containing a high concentration of Vitamin A

Typical stability performance in terms of retention time after a storage time of 4 weeks at 40°C and 75 % rH for the cross-linked beadlets of Example 1 and Example 2 are about 90-95 % which is comparable to standard cross-linked vitamin A forms containing 500'00 IU vitamin A/g active ingredient.

Example 4: Preparation of beadlets containing 1,000,000 IU vitamin A/g beadlet

Approximately 100 parts of gelatine Bloom 140 and 20 parts of fructose were dissolved in 308.2 parts of water (containing 13.2 parts of glycerin) by heating at 65°C. 170 parts of

Vitamin A containing 24% ethoxyquin (assay 2.1 Mio. IU vitamin A per g) were then mixed with the resulting matrix, followed by pre-emulsification.

The beadlet was sprayed using as finely dispersed powder calcium silicate. The average particle size of the beadlet was in the range of from 200µm to 300µm.

The beadlets of 3 lots were treated by a continuous flash treatment in diluted phase wherein the flash treatment is ensured by a combination of pneumatic transport and mechanical transport. The results are compared in the following table:

	Lot 1	Lot 2	Lot 3
Vitamin A content after crosslinking (IU/g)	1'064'808	1'051'641	1'077'224
Vitamin A Loss (%)	<1	<1	<1
Surface vitamin A (%)	3.7	4.0	3.5
Crosslinking grade (%)	60-85	60-85	60-85

In the flash treatment, the beadlet was treated for 1 to 5 minutes at a temperature raising from 105°C to 115°C.

Example 5: Stability of beadlets containing a high concentration of Vitamin A

Typical stability performances in terms of retention time after a storage time of 4 weeks at 40°C and 75 % rH for the cross-linked beadlets of Example 4 are about 95-100 % which are comparable to standard cross-linked vitamin A forms containing 500'00 IU vitamin A/g active ingredient.

Example 6: Preparation of beadlets containing 1,000,000 IU vitamin A/g beadlet plus 200,000 IU vitamin D_3/g beadlet

Approximately 90 parts of gelatine Bloom 140 and 18 parts of fructose were dissolved in 313.2 parts of water (containing 23.2 parts of glycerin) by heating at 65°C. 158 parts of Vitamin A containing 24% ethoxyquin (assay 2.1 Mio. IU vitamin A per g) and 3.5 parts of vitamin D_3 (assay 20 Mio. IU vitamin D_3 per g) were then mixed with the resulting matrix, followed by pre-emulsification.

The beadlet was sprayed using as finely dispersed powder calcium silicate. The average particle size of the beadlet was in the range of from 200µm to 300µm.

The beadlets of 3 lots were treated treated by a continuous flash treatment in diluted phase wherein the flash treatment is ensured by a combination of pneumatic transport and mechanical transport. The results are compared in the following table:

	Lot 1	Lot 2	Lot 3
Vitamin A content after crosslinking (IU/g)	1'105'039	1'074'633	1'077'470
Vitamin D3 content after crosslinking (IU/g)	218'617	214'813	217'858
Vitamin A Loss (%)	<1	<1	<1
Surface vitamin A (%)	4.7	4.7	4.6
Crosslinking grade (%)	60-85	60-85	60-85

In the flash treatment, the beadlet was treated for 1 to 5 minutes at a temperature raising from 105°C to 115°C.

Example 7: Stability of beadlets containing a high concentration of Vitamin A and D3

Typical stability performances in terms of retention time after a storage time of 4 weeks at 40°C and 75 % rH for the cross-linked beadlets of Example 6 are about 95-100 % and about 100% for vitamin A and D3 respectively, which are comparable to standard cross-linked vitamin AD3 forms containing 500'00 IU vitamin A/g and 100'000 IU vitamin D3/g active ingredient.